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REVIEW ARTICLE

Diagnosis of cholangiocarcinoma

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Abstract
Cholangiocarcinoma is suspected based on signs of biliary obstruction, abnormal liver function tests, elevated tumor markers (carbohydrate antigen 19-9 and carcinoembryonic antigen), and ultrasonography showing a bile stricture or a mass, especially in intrahepatic cholangiocarcinoma. Magnetic resonance imaging (MRI) or computed tomography (CT) is performed for the diagnosis and staging of cholangiocarcinomas. However, differentiation of an intraductal cholangiocarcinoma from a hypovascular metastasis is limited at imaging. Therefore, reasonable exclusion of an extrahepatic primary tumor should be performed. Differentiating between benign and malignant bile duct stricture is also difficult, except when metastases are observed. The sensitivity of fluorodeoxyglucose positron emission tomography is limited in small, infiltrative, and mucinous cholangiocarcinomas. When the diagnosis of a biliary stenosis remains indeterminate at MRI or CT, endoscopic imaging (endoscopic or intraductal ultrasound, cholangioscopy, or optical coherence tomography) and tissue sampling should be carried out. Tissue sampling has a high specificity for diagnosing malignant biliary strictures, but sensitivity is low. The diagnosis of cholangiocarcinoma is particularly challenging in patients with primary sclerosing cholangitis. These patients should be followed with yearly tumor markers, CT, or MRI. In the case of dominant stricture, histological or cytological confirmation of cholangiocarcinoma should be obtained. More studies are needed to compare the accuracy of the various imaging methods, especially the new intraductal methods, and the imaging features of malignancy should be standardized.

Current review

The published literature has been reviewed after a systematic search in PubMed for the terms "cholangiocarcinoma", "diagnosis", and "imaging". This review includes current consensus statements [1,2], meta-analysis [3], published clinical guidelines [4], and information systems [5,6]. Recommendations are based on the levels of evidence according to the National Comprehensive Cancer Network (NCCN) [4].

Clinical features of cholangiocarcinomas

Cholangiocarcinomas occur in the hilar region in about 65% of cases, in the distal common bile duct in 20%, and as an intrahepatic lesion in 15% [7,8]. Macroscopically, cholangiocarcinomas are usually categorized in three types: exophytic or mass-forming, infiltrative or periductal, and polypoid or intraductal [9]. This last-mentioned type, also known as biliary papillomatosis or intraductal papillary mucinous neoplasm of the bile ducts (IPMN-B), has a better prognosis than the other two types [10,11]. Histologically, IPMN-B resembles intraductal papillary neoplasm of the pancreas.

Patients with hilar and extrahepatic cholangiocarcinomas usually present with symptoms of biliary obstruction, including painless jaundice, pale stools, dark urine, and pruritis.

Other symptoms that occur in patients with cholangiocarcinomas include malaise, weight loss, and abdominal pain. These non-specific symptoms usually appear after the disease is advanced, but may be the only symptoms in patients with intrahepatic cholangiocarcinomas. Cholangitis is an unusual presentation [1,12]. Hepatomegaly, tumor mass, or dilated gallbladder may be observed at clinical examination.

In patients with primary sclerosing cholangitis, cholangiocarcinoma can be suspected when the patient complains of increasing jaundice, pruritis, weight loss, and abdominal pain, or when a rapidly increasing serum bilirubin level is observed [8]. However, these symptoms are not more frequent in patients with cholangiocarcinoma than in those without malignancy, except when cholangiocarcinoma is detected

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within one year of the diagnosis of primary sclerosing cholangitis [13,14].

Laboratory studies

Biochemical tests typically suggest biliary obstruction, with elevations in total and direct bilirubin, alkaline phosphatase, 5′-nucleotidase, and gamma-glutamyltransferase. Aspartate aminotransferase and alanine aminotransferase may be normal initially. Chronic biliary obstruction often leads to hepatic dysfunction with elevated aminotransferases [5].

Tumor markers

The value of tumor markers in the diagnosis of cholangiocarcinomas remains controversial. The most commonly used markers are carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). In patients with sclerosing cholangitis, the reported sensitivity and specificity of elevated CA 19-9 levels are 50%–100% and 50%–98%, respectively [8]. Various cut-off values have been proposed, generally between 100 U/ml and 200 U/ml. In a recent retrospective study of 208 patients with sclerosing cholangitis, including 14 patients with cholangiocarcinoma, Levy et al. [15] observed that CA 19-9 had an area under the ROC curve of 0.95 for diagnosing cholangiocarcinoma, giving a sensitivity of 79% and a specificity of 98%, with a cut-off value of 129 U/ml. However, in this series, only two of the 14 patients with cholangiocarcinoma were candidates for intervention with intent to cure. This means that CA 19-9 only identifies patients with advanced, unresectable cholangiocarcinomas. This conclusion has been reinforced in a recent study in patients with primary sclerosing cholangitis. In this study, 6 of the 8 patients with primary sclerosing cholangitis and cholangiocarcinomas had early-stage tumors. The AUROC of CA 19-9 in this study was only 0.655. In patients without primary sclerosing cholangitis, the sensitivity of a CA 19-9 level above 100 U/ml in diagnosing cholangiocarcinoma is 53%–67%, with a specificity of 76%–87% [16–18].

High levels of CEA are often observed in gastrointestinal cancers, especially in colorectal carcinomas. High CEA levels may also be observed in cholangiocarcinomas. Several authors have suggested that the diagnostic yield of CEA in the detection of cholangiocarcinoma is lower than that of CEA [18]. The reported sensitivity and specificity of CEA are 33%–84% and 33%–100%, respectively [18,19]. The usual cut-off is 5 ng/ml. The combined use of CEA and CA 19-9 may improve the diagnosis of cholangiocarcinoma [20], but this has not been reproduced in all studies [21]. Both CEA and CA 19-9 have been measured in bile from patients with benign and malignant bile duct diseases, but results are contradictory and no consistent differences have been found [18]. It is concluded that both CA 19-9 and CEA can be elevated in cholangiocarcinoma. However, these markers can be elevated in other cancers, in cholestasis in the absence of malignancy and following liver injury, and, moreover, they have a rather low sensitivity, especially CEA. Therefore, measurements of CA 19-9 and CEA should not be used alone for diagnosing cholangiocarcinomas [1,16,22]. In unexplained biliary disease, CA 19-9 levels >100 UI/ml are considered suspicious for cholangiocarcinoma in the absence of an inflammatory process [18]. In patients with primary sclerosing cholangitis, yearly surveillance with CA 19-9 is carried out at many centers and a cut-off value of 180 UI/ml is often used even if patients with CA 19-9 above this level may already have advanced cholangiocarcinomas [8,23].

In patients with chronic hepatitis C, intrahepatic cholangiocarcinoma or combined hepatocarcinoma and cholangiocarcinoma may cause elevated alpha-fetoprotein levels [24]. It has been estimated that about 10% of hepatic masses with elevated lectin-reactive alpha-fetoprotein levels are cholangiocarcinomas or combined hepatocarcinomas and cholangiocarcinomas rather than hepatocarcinomas [25].

Finally, several new, potentially useful tumor markers, including mucins (MUC5AC) [26], are being studied [27] and serum proteomic profiling is producing encouraging results [28]. The utility of these methods awaits further evaluation.

Imaging

Ultrasonography

Ultrasonography is usually the first examination for biliary obstruction or suspected liver disease. Intrahepatic cholangiocarcinoma may be identified as mass lesions. In contrast, hilar and extrahepatic cholangiocarcinoma are often infiltrative lesions that are difficult to detect. At ultrasonography, non-union of the dilated right and left hepatic ducts may be seen without an identifiable mass [9,29]. However, nodular or irregular wall-thickening and polypoid intraluminal masses may be seen. The reported sensitivity of ultrasonography in detecting ductal masses or mural thickening in hilar and extrahepatic cholangiocarcinoma is up to 87%–96% in some series, but depends on the skill of the investigator [30,31]. The specificity is unknown.

Computed tomography

Computed tomography (CT) can show bile duct dilatation and a tumor mass, bile duct wall thickening, or intraductal tissue in exophytic, infiltrative, and polypoid cholangiocarcinomas, respectively. Multidetector CT may challenge the role of magnetic resonance imaging (MRI) in the diagnosis of

cholangiocarcinoma because of its high spatial resolution [32,33]. Hyperenhancement of the stenosed duct during the portal venous phase has been considered to be a sign of malignancy, but has a low specificity (19%) as an isolated finding [34,35].

Magnetic resonance imaging

MRI with magnetic resonance cholangiopancreatography (MRCP) is usually considered the modality of choice in the diagnosis of cholangiocarcinoma because of its high contrast resolution, multiplanar capability, and its ability to determine the parenchymal, biliary, and vascular extension [23]. Several studies, including a meta-analysis, have shown that MRI has a sensitivity and a specificity >90% in diagnosing biliary obstruction [3,36,37]. The accuracy of MRI in diagnosing a malignant biliary stricture is lower and variable according to the authors (sensitivity of 48%–88% and specificity of 71%–95%) [3,36,38,39]. It is important to perform conventional unenhanced and contrast-enhanced MRI in addition to MRCP to differentiate between benign and malignant bile duct strictures [40].

Intrahepatic cholangiocarcinomas are often exophytic masses that are large when discovered. The lesions are hypointense relative to liver parenchyma on T1-weighted images. On T2-weighted images, they are slightly hyperintense when containing abundant fibrosis and strongly hyperintense when containing mainly necrosis or mucous secretion [41]. On gadolinium-enhanced MRI, the lesions are hypovascular and show progressive and concentric filling with contrast material. Associated findings include hepatic capsular retraction, vascular encasement that may lead to lobar atrophy, and dilatation of peripheral bile ducts. An intrahepatic cholangiocarcinoma may be difficult to differentiate from a metastasis (especially a metastasis from a foregut adenocarcinoma) at imaging and at histology [9]. When an intrahepatic mass presumed to be a cholangiocarcinoma is observed at imaging, upper and lower gastrointestinal endoscopy has been recommended to exclude an extrahepatic primary gastrointestinal tumor [4]. At histology, immunostaining for cytokeratins 7 and 20 helps to differentiate between intrahepatic cholangiocarcinoma and metastasis from colon cancer [42]. An inflammatory pseudotumor may also sometimes be difficult to differentiate from an intrahepatic cholangiocarcinoma at imaging, but may regress spontaneously [43].

Endoscopic ultrasound

It has been reported that endoscopic ultrasound (EUS) improves the diagnosis between malignant and benign strictures relative to MRCP and CT [36,44]. Endoscopic ultrasound can be used for fine-needle aspiration of strictures with variable reported sensitivities of 25%–91% and specificities of 89%–100% [45–49].

Cholangiography

Because of their invasiveness, endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography are replaced by MRCP, CT, and EUS in assessing the morphology of the bile ducts in patients with suspected biliary obstruction [2,50]. To distinguish benign from malignant biliary strictures, however, ERCP can be used to provide tissue samples with different methods, including brush cytology, fine-needle aspiration, and transpapillary biopsy. These sampling methods are highly specific (100%) for diagnosing a malignant tumor, but have a low sensitivity of 46%–73% [19,39,51,52]. The sensitivity can be improved by combining the sampling methods at the expense of an increase in the duration of the procedure and an increase in the needed expertise [53–55]. Moreover, the negative predictive value remains low. The sensitivity of brush cytology can be further improved by detecting chromosomal abnormalities with advanced cytological methods, including digital image analysis and fluorescence *in situ* hybridization [56].

Intraductal ultrasound, cholangioscopy, and optical coherence tomography

Emerging intraductal imaging methods include intraductal ultrasound, cholangioscopy, and optical coherence tomography. Intraductal ultrasound has high sensitivity and specificity in the diagnosis of malignant biliary strictures (sensitivity 89%–95%, specificity 86%–91%) [38,39,44,57,58].

Peroral cholangioscopy has been less studied. Only the surface of the lesions is analyzed with this method, which is further limited by the fragility of the cholangioscopes [59]. Biopsies can be performed through the cholangioscope, but adequate sampling remains challenging because of the small size of the instruments and the limited maneuverability of the long baby endoscope [59,60]. Alternatively, percutaneous transhepatic cholangioscopy can be performed, but a large transhepatic access is needed [61].

Optical coherence tomography is a new optical imaging method. It is analogous to ultrasound imaging but uses infrared light rather than acoustic energy. Optical coherence tomography has an axial resolution of 10 μm, i.e. 10-fold better than that of high-frequency ultrasound. However, its depth penetration is limited to approximately 1 mm versus 10 mm for a 20 MHz ultrasound probe. Only preliminary results on the use of optical coherence tomography in the biliary tree are available [62].

The use of these intraductal diagnostic methods should be further validated by assessing their reproducibility, standardizing the diagnostic features of

malignancy, and comparing the accuracy of the different techniques [63,64].

Positron emission tomography

Fluorodeoxyglucose positron emission tomography (FDG PET) permits the detection of cholangiocarcinomas because of the high uptake of glucose and the low activity of glucose-6-phosphatase in cholangiocarcinoma [65]. Several studies have shown a sensitivity and specificity >90% for PET in the diagnosis of cholangiocarcinomas [66–69]. However, it has recently been recognized that the sensitivity of PET is limited in small, infiltrative, and mucinous cholangiocarcinomas [65,70,71]. In the study by Anderson et al. [65], the sensitivity of PET was 85% in nodular cholangiocarcinomas, but only 18% in infiltrative cholangiocarcinomas. As many hilar and extrahepatic cholangiocarcinomas are infiltrative, these tumors are not readily detected with PET. PET has a reported specificity of 80%–100% [65,67,68]. A much lower specificity of 33% has been reported by Petrowsky et al. in extrahepatic cholangiocarcinomas [71]. The specificity of PET is limited because infectious and inflammatory lesions may show a high FDG uptake [70]. The use of delayed imaging 2 h after injection of the tracer has been recommended to differentiate cholangiocarcinomas from inflammatory lesions [72,73].

Globally, the accuracy of PET was not better than that of CT in the Petrowsky et al. study [71]. The use of PET to diagnose cholangiocarcinomas in primary sclerosing cholangitis remains controversial [69,74]. Because of false-positive and false-negative results, Fevery et al. [74] consider that PET is not a reliable method for the early diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis. Rather than being useful for the diagnosis of cholangiocarcinoma, PET (PET/CT) is particularly valuable in detecting unsuspected distant metastases [71].

Characterization of proximal biliary stenoses

Isolated hilar obstruction not caused by trauma or lithiasis is often malignant and presumed to correspond to cholangiocarcinoma. However, non-traumatic inflammatory strictures may occur and are difficult to differentiate from malignancy [75,76]. At CT and MRI, signs of malignancy include an abrupt, irregular, and asymmetric stricture, a mass lesion or eccentric thickening of the bile duct (>3 mm) with hyperenhancement during the portal venous phase, vascular invasion or stenosis, lymph node enlargement and metastases [36,77]. However, with the exception of metastases, isolated imaging features are not specific. In some studies, it has been reported that up to 27%–75% of the patients with benign proximal biliary strictures had a discrete mass at imaging [75,76,78]. It is therefore important to assess the combination of imaging findings to improve the diagnostic accuracy [77].

"Local" imaging methods, including EUS and intraductal imaging, may improve the differentiation between benign and malignant strictures, mainly by better showing the penetration of the tumor into surrounding tissue. Rosch et al. [36] studied 50 patients with suspected biliary strictures. The sensitivity for diagnosing malignancy of MRCP (90%), CT (90%), EUS (80%), and ERCP (90%) did not differ significantly, nor did specificity (65%, 55%, 80%, and 70%, respectively). By contrast, in the study by Domagk et al. [38], which included 30 patients with suspected biliary strictures, there were significant differences in sensitivity between MRI (48%), CT (76%), EUS (81%), and ERCP with intraductal ultrasound (95%). The specificity of the different imaging methods did not differ significantly (78%–89%). These studies have limitations. Patients with biliary and pancreatic lesions were included. The MRI examinations did not include contrast-enhanced sequences and some examinations were performed after stent placement.

Further studies are needed to assess the role of the imaging methods in differentiating between benign and malignant strictures. However, when a doubt exists about the diagnosis of a proximal biliary stricture at CT or MRI, "local imaging" should be performed because it has high spatial resolution and offers the possibility of tissue sampling.

Conclusions

The diagnosis of cholangiocarcinoma remains difficult, despite the multiple diagnostic methods available. Further studies comparing the accuracy of the various imaging methods, especially the new intraductal methods, are needed, and the imaging features of malignancy should be standardized. Currently, no single imaging method emerges for the diagnosis of cholangiocarcinoma. Because no high-powered randomized clinical trials are available for assessing the accuracy of the various methods in the diagnosis of cholangiocarcinoma, and only limited evidence comes from meta-analysis, the quality of evidence is low (category 2A according to the NCCN categories of evidence).

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